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THE PROPER TIME TO COLLECT SANGUINARIA.

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In the September issue of the AMERICAN JOURNAL OF PHARMACY for 1913 there appeared a paper by Drs. Homerberg and Beringer on the proper time to collect Sanguinaria. The time suggested, "About or immediately after flowering," was based upon the results of assays of the drug "collected at various times from May—just after flowering—to August—just before the leaves began to die."

But as the time of collection of the samples assayed did not cover that period of the year specified by the U. S. P. for its collection, *i.e.*, "After the death of the foliage," it was thought desirable to make various collections during this period in order to supplement and make more complete the work carried out by Drs. Homerberg and Beringer. Accordingly, samples of the rhizome were collected at various times during the ensuing year which covered both the active and quiescent periods of the species. The rhizomes were carefully cleaned, the rootlets removed, and air-dried in the shade at ordinary room temperature; the last collection, however, was dried artificially. The rootlets were kept separately until the close of the experiment, when they were mixed together and assayed. They yielded 1.77 per cent. *sanguinarine,* thus averaging about one-third the amount obtained from the rhizomes.

The results obtained confirm in all respects those obtained by Drs. Homerberg and Beringer, indicating that the best time to collect the rhizome, which should be freed of rootlets, is at the flowering season.

The commercial drug can be readily separated on gross internal characters into three grades, probably representing three species:

A. This grade breaks with a short, waxy fracture, showing a white ground plentifully sprinkled with red resin cells.

B. This grade breaks with a short fracture, showing a rather soft, more or less mealy surface of a brick-red or orange color, the resin cells not being perceptible to the naked eye.

C. This grade breaks with a short, waxy fracture, and shows a liver-brown or reddish-brown color.

The rhizomes collected for experimental work were of typical *Sanguinaria canadensis* Lin., and corresponded to grade *A* as above outlined; the commercial drug assayed for comparison showed a higher percentage of alkaloid than that specially collected.

The assays were made by Mr. J. B. Williams, of the Scientific Laboratory.

ASSAY OF COMMERCIAL DRUG, SANGUINARIA.

Grade	Moisture, per cent.	Sanguinarine, per cent.
A	6.68	6.95
B	6.80	6.01
C	6.6	7.01

ASSAY OF COLLECTED SAMPLES OF AIR-DRIED SANGUINARIA.

Time of collection	Moisture, per cent.	Sanguinarine per cent.
11/13/13	79.84	4.75
1/16/14	78.71	4.70
3/18/14	84.24	4.84
4/16/14 (Flowering season)	85.54	6.53
5/28/14 (Fruiting season)	79.20	5.10
6/19/14 (After fruiting season)	76.50	5.00
7/30/14 (Just after death of foliage)	76.12	5.00
10/29/14 Artificially dried	79.88	4.93

ASSAY OF COLLECTED SAMPLES OF AIR-DRIED ROOTLETS OF SANGUINARIA.

Time of collection	Moisture, per cent.	Sanguinarine, per cent.
November, 1913, to July, 1914	79.5	1.77

BELLADONNA AND HYOSCYAMUS.

By OLIVER A. FARWELL, Department of Botany, Parke, Davis & Co., Detroit, Mich.

Much has been written of late about the cultivation of belladonna and hyoscyamus for commercial purposes. It has been shown that belladonna is hardy as far north as New York. Henbane is a much hardier plant and is known to be well established on Mackinac Island, in the Straits of Mackinac, between the two peninsulas

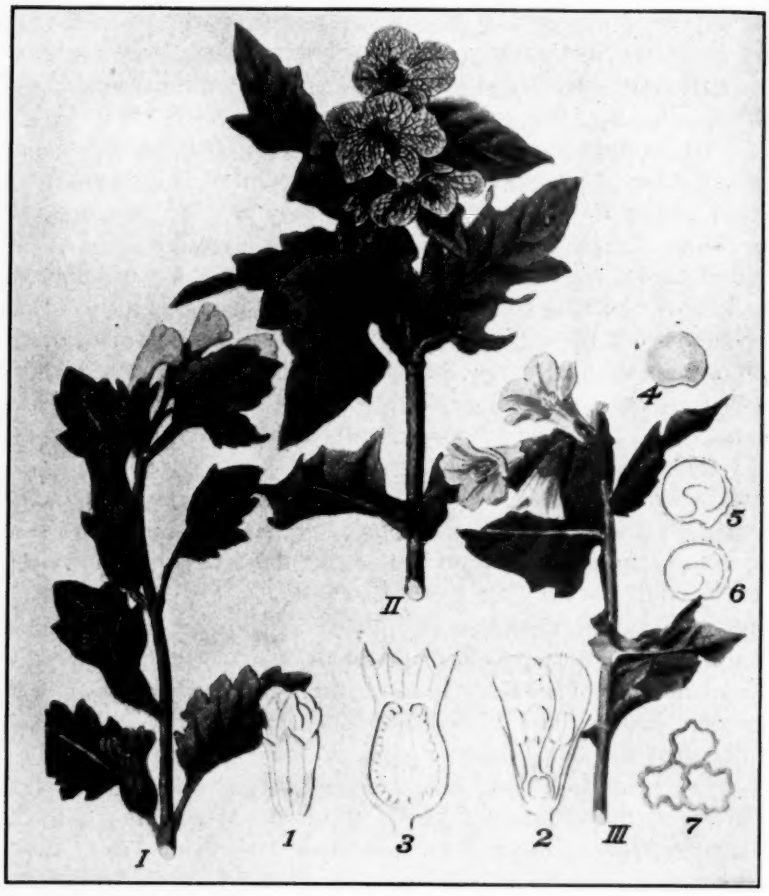
of Michigan, and on the adjacent mainland on either side. Belladonna is hardy at Detroit, where it maintained a foothold for many years on ballast grounds until exterminated by the processes of economic improvements. It has also been under cultivation for several years, and is still in a flourishing condition, having weathered the cold winters of zero temperature and below without any protection and seemingly without injury to the vigor of the plants.

Seeds of the annual *Hyoscyamus Bohemicus* obtained from commercial drug, together with seeds and seedlings of *Atropa Belladonna* and of the biennial *Hyoscyamus niger* procured several years ago from the Department of Agriculture, were sown and transplanted, and these or their descendents are still producing flourishing growths. The seeds of belladonna sown in the garden did not germinate, but the self-sown seed from the plants germinated the following spring in large numbers. Individuals of the biennial henbane often have corollas that are veined with brownish green or olive instead of violet or purple, even on the same plant, and the contrast is rather striking.

In view of the fact that the henbanes are subject to destructive attacks by the common potato bug, *Doryphora decemlineata,* and the allied, three-lined potato-bug, *Lema trilineata,* it would seem that its cultivation for commercial purposes in this country will not meet with any degree of success, as the cost of keeping the plants free from these pests would make the price of the drug prohibitive. Belladonna is not so liable to be attacked, last year (1914) being the first season since their cultivation began (1910) that these plants were infested by insect pests.

In a recent paper on belladonna and hyoscyamus, published in this JOURNAL by Professor Newcomb, of the Minnesota College of Pharmacy, *Hyoscyamus albus* is illustrated by two figures. From a taxonomic point of view, at least, these figures, as representative illustrations of *Hyoscyamus albus* Lin., are open to criticism. If compared with the accompanying figure, which is a reproduction of plate 2 of vol. 20 of Richenbach's *Icones,* showing *H. niger, H. albus,* and *H. pallidus,* it will at once be seen that they show no strain of *H. albus,* a species more closely related to *H. aureus* than to *H. niger. H. albus* differs widely in its nearby *orbicular* leaves, all of which are *petioled,* and in its *prominently peduncled flowers* and *fruits,* the *calyces* of which are of a different shape; none of these

characters appear in the figures referred to, which, however, do compare very favorably with that of *H. pallidus,* and this, it is very evident, is what they represent. Undoubtedly Professor Newcomb



Photographic reproduction of Plate 2 in vol. XX Reichenbach's Icones Floræ Germanicæ et Helveticæ. I, *Hyoscyamus albus* L.; II, *Hyoscyamus niger* L.; III, *Hyoscyamus niger* L. var. *pallidus* Koch. 1, Alabastrum, ut videas æstivationem imbricatem; 2, Flos transsectus; 3, Fructus transsectus vides operculum pyxidis; 4, Semen; 5, 6, Semina transsectus; 7, Areæ testæ.

has placed too much reliance upon the authenticity of the nomenclature adopted by seedsmen, for his figure of *H. albus* shows that he has received seed improperly named, a state of affairs which is not at all uncommon in the trade.

Professor Newcomb's experiments developed no tendency in the biennial hyoscyami to become annual or *vice versa,* which is in accordance with my own observations covering a period of several years. These species might, therefore, be better understood if the annual and biennial forms are maintained as distinct species. Under these conditions, *Hyoscyamus niger* Lin. will be restricted to the large, branched, biennial plant having yellow flowers, with violet, purple, or brownish-green veins. The annual plant, with similarly colored flowers, but with a slender, generally unbranched stem, will then be known as *H. Bohemicus* F. W. Schmidt, of which the yellow-flowered *H. pallidus* Wald. and Kit. becomes a color variety.

The proper names and leading synonyms are as follows:

HYOSCYAMUS NIGER Lin. Sp. Pl. 179, 1753. Probably belonging here are:

H. officinarum Crantz Inst. 2, 325, 1766.

H. lethalis Salisb. Prod. 131, 1796.

HYOSCYAMUS BOHEMICUS F. W. Schmidt, Fl. Bohem. 3, 31, 1795.

H. Verviensis Lejune, Fl. de Spa. 1, 116, 1811.

H. agrestis Kit. in Schult. Œster. Fl. Ed. 2, 1, 383, 1814.

H. pictus Roth Nov. Pl. Sp. 119, 1821.

H. niger Lin. var. *annua* Sims. Bot. Mag. t. 2394, 1823.

H. niger Lin. var. *agrestis* Nees ab Es. Trans. Lin. Soc. 17, 77, 1837.

HYOSCYAMUS BOHEMICUS Schmidt var. PALLIDUS (Wald. and Kit.) N. Comb.

H. pallidus Wald. and Kit. Plant. Rar. Hung. ex Willd. Enum. Hort. Berol. 227, 1809.

H. niger Lin. var. *pallidus* Koch Syn. 509, 1837.

ESTIMATION OF CINEOL IN OIL OF EUCALYPTUS.[1]

By JOSEPH L. TURNER and RALPH C. HOLMES.

The question of an accurate determination of the quantity of cineol in oil of euclayptus is still unsettled, notwithstanding the quite considerable amount of research which has been devoted to it, and, judging from its present status, it will not be settled for some time to come. This is to be regretted the more since it is now established beyond dispute that the value and therapeutic action of

[1] Read at the November meeting of the New York Branch of the American Pharmaceutical Association.

eucalyptus oils depend exclusively upon their content of cineol (eucalyptol). Various methods proposed heretofore, without exception, suffer from one shortcoming—gross inaccuracy; either due to the wrong basis of method, or to the instability of those compounds which have been suggested as serviceable for the separation of cineol.

To the class of methods based on wrong premises belong the "Permanganate Method" proposed by Francis D. Dodge (*Journal Industrial and Engineering Chemistry,* vol. iv, August, 1912, p. 529) and the "Resorcinol Method" proposed by Schimmel & Co. (Semi-annual Report of Schimmel & Co., October, 1907); the latter method is now slated for inclusion in the Ninth Revision of the United States Pharmacopœia, and it will thus become responsible for the admission into the pharmaceutical practice of inferior eucalyptus oils, as we propose to show further below.

The methods based on the separation of unstable addition products of cineol are: the phosphoric acid method and the hydrobromic acid method.

The various methods mentioned will be outlined briefly, as it is not our purpose here to enter into a thorough discussion of these. Exhaustive information, both *pro* and *con,* may be obtained from the literature on the subject, and especially by perusing the semi-annual reports of Schimmel & Co.

1. *Phosphoric Acid Method.*—"Introduce into a beaker a solution prepared by dissolving 10 Cc. of oil of eucalyptus in 50 Cc. of purified petroleum benzin; immerse the beaker in a freezing mixture and add phosphoric acid, drop by drop, with constant stirring, until the white magma of cineol phosphate formed begins to assume a yellowish or pinkish tint; then transfer the magma to a force filter, wash it with cold, purified petroleum benzin, and then dry it by pressure between two porous plates. Transfer the precipitate (cineol phosphate) to a narrow graduated cylinder, and add warm water, which will cause separation of the cineol. The volume, in cubic centimetres, of the separated oil, multiplied by 10, represents the volume per cent. of cineol (eucalyptol)."

The addition product of eucalyptol with phosphoric acid, as obtained by this method, is a semi-solid, sticky substance which decomposes very readily and renders a quantitative separation very difficult, if not altogether impossible. In consequence of this, the results obtained by this method are invariably too low.

2. *The Hydrobromic Acid Method* is carried out as follows: "In a highly cooled solution (freezing mixture) of 10 Cc. eucalyptus oil in 40 Cc. low-boiling petroleum ether (boiling-point about 40°) *absolutely dry* gaseous hydrobromic acid is introduced until a precipitate is no longer formed. The pure white hydrobromide of cineol formed is rapidly collected with a suction pump and washed with cold petroleum ether. Into the filtered-off liquid hydrobromic acid is again introduced; any precipitate formed is collected separately, and then added to the bulk. For the purpose of removing the petroleum ether, the cineol hydrobromide is left standing for a quarter of an hour in a vacuum; it is then rinsed with a little alcohol into a cassia flask and decomposed with water. The cineol separated off is brought into the neck of the flask by the addition of more water, and the quantity of the oil read off the scale. By multiplying with 10, the cineol content of the oil employed is obtained in per cent. by volume."

This method has the same drawback as the phosphoric acid method, namely, rapid decomposition of the addition product. Moreover, the procedure for obtaining the cineol hydrobromide is a very complicated one, and is not suitable, therefore, for ordinary practical purposes.

3. *The Potassium Permanganate Method* is based upon the fact that, in the cold, cineol remains practically unattacked by potassium permanganate, whereas the remaining constituents of the oils in question (eucalyptus oil and cajuput oil) are oxidized into soluble compounds. The process is carried out as follows: "10 Cc. of the oil under examination are placed in a narrow-necked flask, cooled with ice-water, and shaken with a gradually added 5 to 6 per cent. solution of potassium permanganate until the latter is present in excess. The mixture is then left standing in ice-water for from 12 to 18 hours with occasional shaking, after which the manganese peroxide which has separated out is brought to solution by means of a careful addition of sulphurous acid (or sodium bisulphite + hydrochloric acid). The unattacked oil (eucalyptol) is brought into the neck of the flask, pipetted into a graduated tube, washed with a little alkali, and estimated volumetrically. Its specific gravity should be 0.929 to 0.930 (15°); it should be inactive, and dissolve in 3.5 volumes 60 per cent. alcohol at 25°."

We have not investigated this method personally, but are rather willing to accept the criticism as published in Schimmel & Co.'s

Semi-annual Report, for April, 1913, p. 62, containing results of experiments on known mixtures of cineol with pinene, which, when estimated by this method, showed a cineol content of 95 per cent.; a mixture of 50 per cent. cineol and 50 per cent terpineol, on the other hand, yielded only 30 per cent. cineol. Time does not permit us to enter into a more complete discussion of these results.

4. *Resorcinol Method,* or, more correct, *Resorcinol Methods,* since there is an " original " method as described in Schimmel & Co.'s Report for October, 1907, in Gildemeister & Hoffmann's " Volatile Oils," 1913, p. 601, and as proposed for the inclusion in the Ninth Revision of the U. S. Pharmacopœia, and also a " Modified Resorcinol Method " as given in Schimmel & Co.'s Report for April, 1908.

The " original " method is based on the fact that cineol forms an addition produced with resorcinol, which is soluble in an excess of concentrated resorcinol solution.

The process is carried out as follows: " To 10 Cc. of oil contained in a 100 Cc. cassia flask enough 50 per cent. resorcinol solution is added to fill the flask about four-fifths. For five minutes the mixture is thoroughly shaken, and the portion of the oil which has not gone into solution is driven into the neck with resorcinol solution. Any oily particles adhering to the walls of the flask are caused to rise to the surface by rotating the flask or gently tapping it. After the resorcinol solution has become perfectly clear, which usually requires several hours, the volume of oil remaining is read off, the cineol content ascertained by subtracting this amount from 10, and the resultant multiplied with 10 in order to obtain the percentage by volume. Oils very rich in cineol are advantageously diluted with an equal volume of turpentine oil, since the cineol-resorcinol occasionally crystallizes from concentrated solution, thus rendering futile the entire process."

It soon became apparent, however, that this method gave too high results, for the reason that constituents of eucalyptus, other than cineol, are also soluble in the resorcinol solution, and further investigation of the subject led to the " Modified Resorcinol Method," which consists in distilling the oil of eucalyptus at such a rate that only one drop distils over in one second, collecting the portion distilling between 170° and 190° C., and subjecting this portion to the estimation by the above-described resorcinol method.

We have examined a number of oils both by the "original" and "modified" Resorcinol Methods, and have reserved our criticism of these for the latter part of our paper.

Many a chemist's patience has been sorely tried by the phosphoric acid method of separating cineol, as outlined in the U. S. P. VIII; and, therefore, the resorcinol method, as proposed originally by Schimmel & Co. and as described in the last edition of Gildemeister & Hoffmann's "Volatile Oils," seemed to afford an easy and accurate means of estimating cineol. However, it became evident at the first application of this method that the new process was not above suspicion, especially when some eucalyptus oils, persistently refusing to form a semi-solid precipitate with phosphoric acid, showed unusually high cineol content when assayed by the resorcinol method.

The logical idea then suggested itself of trying arsenic acid instead of phosphoric acid, with a view of obtaining a more stable addition product, and the results so obtained exceeded our expectations. Later, a search through the literature revealed the fact that the idea was not original with us, since cineol arsenate became the subject of a patent as early as June 20, 1901 (German Patent No. 132606, U. S. Patent No. 705545), and, according to Thoms & Molle (*Arch. der Pharmazie*, 242 (1904), p. 172), they used arsenic acid in February, 1901, for the purification of cineol, as well as for its separation from various fractions of the oil of bay laurel. Nevertheless, we justly claim the credit for being the first to apply arsenic acid to the *quantitative estimation* of cineol.

We found that by adding, approximately, an equal volume of an 85 per cent. solution of arsenic acid to cineol a white, solid, crystalline substance resulted, which is sufficiently stable to permit handling it in the air, and which is decomposed by hot water into its components; that is, cineol and arsenic acid. A compound obtained by mixing equimolecular quantities of cineol (152.98) and arsenic acid (140.9) was tested for its stability when exposed to air at ordinary room temperature with the following result:

5 hours in open air, temperature 25° C.	Loss, 2.9 per cent.
22 hours in open air, temperature 25° C.	Loss, 6.0 per cent.
29 hours in open air, temperature 25° C.	Loss, 7.0 per cent.
45 hours in open air, temperature 25° C.	Loss, 8.4 per cent.
69 hours in open air, temperature 25° C.	Loss, 9.6 per cent.

The determination of cineol in cineol-bearing oils by means of arsenic acid is carried out as follows:

Deliver from a pipette 10 Cc. of the oil into a glass dish (preferably a round-bottom one) of 50 Cc. capacity, which is imbedded in finely cracked ice. Add 10 Cc. of concentrated arsenic acid (containing about 85 per cent. arsenic acid; see " Note " below) and stir until precipitation is complete. When the mixture ceases to congeal further, allow to stand ten minutes in the ice. *At this point,* if the mixture forms a hard mass, indicating an oil rich in cineol, 5 Cc. of purified petroleum ether should be added, and the mass mixed well; transfer immediately to a hardened filter paper[2] by means of a pliable horn spatula; spread evenly over the surface of the paper and lay a second hardened filter paper over the top. Outside of the hardened filters place several thicknesses of absorbent or filter paper, and transfer the whole to an ordinary letter press, bringing to bear all the pressure possible for about one minute. Change the outside absorbent papers and press again, repeating the operation, if necessary, until the cineol arsenate is apparently dry and separates readily when touched with a spatula. The pressing is *not* complete when a hard mass remains which is broken up with difficulty; the method usually requires two changes of filter paper, pressing each time for about two minutes; if left too long in the press the compound may decompose. Now transfer completely the compound by means of the horn spatula to a glass funnel inserted into a 100-Cc. cassia flask with neck measuring 10 Cc. graduated in 1/10 Cc. Wash the precipitate into the flask with a stream of hot water from a wash bottle, assisting the disintegration with a glass rod. Place the flask in boiling water and rotate until the compound is thoroughly broken up; add enough water to cause the cineol to rise into the neck of the flask, cool to room temperature, and read off the volume; on multiplying the latter by 10 the percentage of cineol in the oil is obtained.

In judging whether or not petroleum ether should be added, the following rule should be observed: Add enough petroleum ether to soften the cineol arsenate so as to obtain a plastic mass; the quantity necessary never exceeds 5 Cc., and decreases with oils containing less than 80 per cent. of cineol. The object of adding petroleum ether

[2] In our work we found most useful Schleicher & Schull's hardened filters No. 575, 18½ cm. diameter.

is merely to soften the hard mass and to aid in the separation of non-cineol constituents of the oil. A large excess of petroleum ether will decompose the compound.

The above method is applicable directly to all oils containing above 50 per cent. of cineol; in oils containing lower proportions of cineol the precipitate is not solid enough to permit of convenient handling; and if the cineol content drops below 25 per cent., the separation of cineol arsenate is not quantitative. We have found that the addition of an equal volume of eucalyptol to such oils (*i.e.*, mixing 5 Cc. of the oil with 5 Cc. of eucalyptol) successfully overcomes this difficulty; it then only becomes necessary to subtract from the volume of cineol, as observed in the neck of the flask, 5 Cc., and to multiply the difference by 10, in order to obtain the percentage of cineol in the oil.

NOTE.—The arsenic acid may be obtained in commerce in crystalline form, and may be dissolved in water in such proportion that the resulting solution has the specific gravity of 2.173 at 25° (corresponding approximately to 85 per cent. arsenic acid), or it may be conveniently prepared in the laboratory as follows:

Place in a porcelain evaporating dish 50 Cc. nitric acid specific gravity 1.142, and add 60 Gms. arsenic trioxide in small portions, stirring continuously; after the reaction becomes less violent, heat over Bunsen burner until the oxidation is complete and the excess of nitric acid is evaporated; test for freedom from both arsenic trioxide and nitric acid; filter and evaporate to about 100 Gms. The resulting solution contains about 85 per cent. of arsenic acid (H_3AsO_4).

In order to test the reliability of the method, we have prepared, to begin with, various mixtures of cineol with turpentine oil, and ascertained their cineol content in the manner above described, with the following results:

1. 50 vol. per cent. cineol + 50 vol. per cent. turpentine oil; found 49.5 per cent.; 50 per cent. cineol.

2. 60 vol. per cent. cineol + 40 vol. per cent. turpentine oil; found 59 per cent.; 60 per cent. cineol.

3. 75 vol. per cent. cineol + 25 vol. per cent. turpentine oil; found 74 per cent.; 75 per cent. cineol.

As stated above, we found that the application of the method to mixtures containing less than 50 per cent. cineol is not practicable; and, since adding cineol to such mixtures would have amounted

simply to testing known mixtures containing a higher percentage of cineol, we have omitted this part of investigation from the line of our work as originally planned.

In order to test the applicability of our method to various oils containing cineol, we have collected from several sources a number of samples of such oils and subjected them to assaying by the arsenic acid method, comparing our results with those obtained by the resorcinol method.

The comparison was carried out both on original oils and on fractions distilling over between 170 and 190° C. as outlined in Schimmel & Co.'s Report, April, 1908 ("Modified Resorcinol Method").

For the purpose of determining the purity of cineol separated by the arsenic acid method, several portions of cineol, obtained in the course of assays of *original* oils, were mixed and subjected to physical examination with the following results:

Specific gravity at 25°C., 0.9218; melting-point, 1° C.; optical rotation, + 0° 13′.

On the other hand, being already familiar with the fact that results obtained by the resorcinol method on original oils are not reliable, we examined only that cineol which was obtained by the "modified resorcinol method," and which was thus subjected to considerable purification, at first by distilling the oil, then by distilling with steam the resorcinol solution containing the soluble portion of the above distillate. Cineol collected in this manner from a number of resorcinol solutions possessed the following properties:

Specific gravity at 25° C., 0.9242; melting-point, −3° C.; optical rotation, + 0° 7′

The criterion of a pure cineol, according to the U. S. P., being specific gravity at 25° C. – 0.921 to 0.923, melting-point – 1° C., and optically inactive, the purity of cineol obtained by the arsenic acid method, as evidenced by its physical properties, shows conclusively that none of the constituents of oil of eucalyptus other than cineol are precipitated by the arsenic acid, and that the precipitate of cineol arsenate can be freed, with comparative ease, from the non-cineol portion of the oil in question.

Results of assays made by us on 18 samples of various oils are incorporated in the following table:

No.	Name of oil	S. G. at 25°	O. R.	Arsenic Acid Method		Resorcinol Method		Remarks
				Direct, per cent.	After distillation, per cent.	Direct, per cent.	After distillation, per cent.	
1	Eucalyptus Globulus...	0.9187	+0°50′	84 82	83	88	88	Boiling-point–174° C.
2	Eucalyptus Austral....	0.9108	+0°43′	78 78	78.8	90	85.5	No distillate below 170°. "Cineol fraction," 95 per cent.
3	Eucalyptus.....	0.9171	.....	85	85	88	88	Distilled completely between 170° and 190° C.
4	Eucalyptus Bosisto.....	0.9158	.....	84	84	90	90	Distilled completely between 170° and 190° C.
5	Eucalyptus Algers.....	0.9176	+5°15	58	49.6	Note	57 55.5	Fraction below 170°—14.6 Cc. contained 8.32 Cc. cineol "Cineol fraction,"—73 Cc. (from 100 Cc. oil).
6	Eucalyptus Austral....	0.9182	.....	84 84	84.48	90	91	No distillate below 170°. "Cineol fraction, "96 per cent.
7	Eucalyptus Amygdalina	0.8640	−44°10′	Note	14.7 14.7 15.6	36	14.7	Distillate below 170°—15 per cent. "Cineol fraction," 82 per cent.
8	Eucalyptus Globulus...	0.9171	.....	85	86	90	89	No distillate below 170°. "Cineol fraction," 95 per cent.
9	Eucalyptus Amygdalina	0.8680	−36°38′	No ppt	5.0 6.0	54	14.8	Distillate below 170°—2.6 per cent. "Cineol fraction," 78 per cent.
10	Eucalyptus Dumosa....	0.9145	.....	78 76	74 75	94	78	No distillate below 170°. "Cineol fraction," 95 per cent.
11	Eucalyptus Globulus...	0.9179	.....	83	84.48	92	91	No distillate below 170°. "Cineol fraction," 96 per cent.
12	Eucalyptus Austral....	0.9254	+4°24′	64 65	63.3	90	66.3	Distillate below 170°—2.6 per cent. "Cineol fraction," 78 per cent.
13	Eucalyptus Austral....	0.9210	.....	77.5 78	78	92	87	No distillate below 170°. "Cineol fraction," 91 per cent.
14	Eucalyptus Austral....	0.9188	.....	83.5	84.5	92	90	No distillate below 170°. "Cineol fraction," 96 per cent.
15	Eucalyptus Austral....	0.9178	.....	82 82 83	83	86	88	No distillate below 170°. "Cineol fraction," 95 per cent.
16	Eucalyptus.....	0.9156	+0°18′	84.5 85	86	88	88	No distillate below 170°. "Cineol fraction" 94.5 per cent.
17	Cajuput Native.....	.....	.....	60 61	49.6 50.7	73	54	No distillate below 170°. "Cineol fraction," 67 per cent. Fraction above 190° contained cineol.
18	Camphor.....	.....	.....	55	53	55	53	Distillate below 170°—22 per cent. (contained cineol). "Cineol fraction," 78 per cent.

NOTE: Insufficient quantity of oil to complete the determination.

Close agreement of results obtained by the arsenic acid method on original oils with those obtained on the distillate, collected between 170 and 190° C., speaks well for their correctness. An additional argument in favor of this contention is the fact that these results, from the very nature of the process, tend to be somewhat high rather than low; observing, at the same time, that results yielded by the modified resorcinol method are invariably higher than those obtained by our method, we must necessarily conclude that the latter represent more nearly the true cineol content of an oil; remembering in addition the almost quantitative yield of cineol from its mixture with various proportions of oil of turpentine when precipitated by arsenic acid (see p. 107), we feel justified in stating that our method gives results which represent the true cineol content within the limit of experimental error, which in this case does not exceed 2 per cent.

We regard the results of our experiments in known mixtures of cineol with oil of turpentine as conclusive, and our method as directly applicable to all varieties of cineol-bearing oils, for the reason that in such oils cineol is the only constituent precipitated by the arsenic acid.

The purity of cineol, as well as the close concordance of results obtained by our method before and after distillation, shows that oxygenated constituents other than cineol are not precipitated by arsenic acid, since fractions distilling above 190° C. carry most of such compounds, and their removal would have resulted in a percentage of cineol lower than that obtained in the assay before distillation, if the opposite were the case.

On the contrary, the numerous experiments carried out by Schimmel & Co. in assaying, by the modified resorcinol method, mixtures composed of cineol and fractions of eucalyptus oil distilling *below* 170 and *above* 190°, do not prove the reliability of this method, since such mixtures do not contain the non-cineol constituents distilling *between* 170 and 190° C., some of which unquestionably are soluble in a 50 per cent. resorcinol solution; the latter may be seen from the fact that, in the large majority of oils examined by us, the resorcinol method (modified) gave higher results than the arsenic acid method.

An additional error in the resorcinol method is contributed by the solubility of oil of eucalyptus in water, which dissolves from 4 to 5 per cent. of this oil, whereas cineol is almost insoluble; it

could not be argued, therefore, that lower results obtained by our method could be due to the solubility of cineol in water.

We have adduced sufficient proof to show that the solubility of certain constituents of cineol-bearing oils must necessarily lead to a higher than actual cineol content when estimated even by the modified resorcinol method; it, therefore, becomes superfluous to discuss the total lack of reliability of the original resorcinol method in the form proposed for the inclusion into the forthcoming edition of the U. S. Pharmacopœia. Some oils, such as eucalyptus amygdalina, may, when assayed by this method, be accepted as a U. S. P. oil of eucalyptus, especially if a small quantity of cineol were added to them. Likewise, oils rich in oxygenated constituents may be freed from a large proportion of their cineol content by freezing and then offered in commerce as a U. S. P. product.

Schimmel & Co., in introducing the modified resorcinol method, assume that the fraction of oil of eucalyptus distilling between 170° and 190° carries all of the cineol contained in the oil. We admit that such an assumption may be correct in the majority of oils; we have encountered, however, some oils in which the presence of cineol was proven in portions distilling either below 170 or above 190° C. (see table, oils No. 5, No. 17, No. 18); in such oils, therefore, a certain portion of cineol would not be included into the estimation. Thus, while the modified method is, in a way, an improvement on the original method, yet, at the same time, it introduces a new source of error.

Among eighteen samples of cineol-bearing oils we found only one in which concordant results were obtained by the resorcinol and arsenic acid methods (see table, oil No. 18). We regard this single exception as a final and conclusive proof of the unreliableness of the resorcinol method in general, and of the superiority of the arsenic acid method.

Summary.

1. Arsenic acid forms with cineol an addition compound which is sufficiently stable for all practical purposes.

2. While the arsenic acid method cannot be included among those scientifically exact methods which give results varying only slightly even in the hands of a novice, nevertheless, we are convinced that this method is superior to any method yet proposed for the determination of cineol, being directly applicable to all cineol-bearing oils,

giving results which are concordant within 2 per cent., and representing, for all practical purposes, the true cineol content of an oil.

3. The resorcinol method, as slated for the U. S. P. IX, should not be adopted by the Revision Committee, for it will unquestionably lead to the introduction into commerce of low-grade eucalyptus oils; it would be far better to retain the present unsatisfactory phosphoric acid method, which undoubtedly is responsible for the fact that the majority of eucalyptus oils at present on the market possess a high cineol content, as seen from the analysis of samples obtained by us. We may suggest, however, that the Sub-committee on Volatile Oils investigate the reliability of the arsenic acid method with the view of including it in the forthcoming edition of the Pharmacopœia.

Research Laboratory, Bristol-Myers Company,
Brooklyn, N. Y.

SOME ASH DETERMINATIONS ON DIGITALIS.[1]

By Edwin L. Newcomb and Manley H. Haynes.

In view of the proposed ten per cent. ash standard for digitalis for the ninth revision of the United States Pharmacopœia, the results of some ash determinations upon this drug are hereby offered for consideration. The results in part represent some of the work done in connection with the production of digitalis at the College of Pharmacy, University of Minnesota.

The fully-matured green leaves of the first year's growth of several varieties of Digitalis purpurea were collected and carefully cleaned, including brushing to remove any adhering sand, and then immediately dried at a temperature of 80° to 100° C. The samples were then reduced to a No. 60 powder and dried at low temperature to practically constant weight, after which they were incinerated in the usual manner.

The details concerning the culture of the plants and the collection and drying of the drug have been earlier reported by one of us (see Newcomb, Amer. Journ. of Pharm., vol. 84, pp. 201–214), and the results of physiologic tests with these samples have been

[1] Read at Thirty-first Annual Convention of Minnesota State Pharmaceutical Association, St. Paul, February 10, 1915.

reported (see 1914 *Proceed. Minn. State Pharm. Assoc.*, pp. 148–158, and *Northwestern Druggist*, vol. 15, No. 7, 1914).

Source of sample	Per cent. of ash	Per cent. of ash	Per cent. of ash
1911 and 1912 crop:			
Digitalis purpurea alba	7.1	7.2	
Digitalis purpurea alba	6.79	6.61	
Digitalis purpurea rosea	12.9	13.1	
Digitalis purpurea monstrosa	9.1	9.5	
Digitalis purpurea, mixed varieties	11.4	11.6	
Digitalis purpurea, mixed varieties	10.5	10.8	
Digitalis purpurea, mixed varieties	10.5	10.3	10.8
Digitalis purpurea, collected in the State of Washington from wild growing plants	14.4	14.39	14.27
1913 crop University of Minnesota:			
Digitalis purpurea, mixed varieties	10.00	10.42	
1914 crop University of Minnesota:			
Digitalis purpurea, mixed varieties	8.57	8.46	
Commercial samples:			
A. Clean commercial sample	12.5	12.8	
B. Clean commercial sample from cultivated plants	9.7	10.5	
C. Average quality commercial sample	7.5	7.4	
D. Average quality commercial sample	9.19	9.27	

The commercial samples examined represented fairly good digitalis, no adulterants being found upon microscopic examination.

From these results it would appear that a pharmacopœial standard for digitalis reading "*Ash not exceeding* 10 *per cent.*" would exclude some samples which without doubt are authentic and of good quality.

Department of Pharmacognosy, College of Pharmacy,
University of Minnesota.

ASH CONTENT OF SOME UNOFFICIAL DRUGS.[1]

By Edwin L. Newcomb.

	Ash, per cent.	
Aralia racemosa:		
Commercial sample of average cleanliness	7.88	7.60
Asarum:		
Clean commercial sample	9.23	9.22
Baptisia:		
Commercial sample of average cleanliness (ash pinkish white in color)	2.293	2.288

[1] Presented at the Thirty-first Annual Convention of Minnesota State Pharmaceutical Association, St. Paul, February 10, 1915.

	Ash, per cent.	
Bryonia:		
A. Clean commercial sample	6.49	6.17
B. Commercial sample powdered Bryonia (This sample, upon microscopic examination, showed numerous stone cells and other tissue not found in true Bryonia.)	12.51	12.63
Castanea:		
Clean commercial sample	3.927	3.958
Coptis:		
Clean commercial sample	5.07	5.06
	4.28	4.91
Convallaria flowers:		
Clean commercial sample, with few flower stalks.... (Ash of a bluish-green color.)	9.68	9.39
Damiana:		
Clean commercial sample	7.40	7.21
Dioscorea:		
Clean commercial sample	3.00	3.078
Iris versicolor:		
A. Commercial sample powdered in our laboratory....	3.03	3.4
B. Sample consisting of the roots alone, from plants grown in the Medicinal Plant Garden	6.00	5.80
C. Sample consisting of the rhizomes alone from plants grown in Medicinal Plant Garden	4.77	4.28
Juglans:		
Clean commercial sample of root bark	7.702	7.396
Menyanthes:		
Commercial sample	9.56	9.46
Myrica:		
Clean commercial sample	3.04	2.86
Euphorbia:		
Select commercial sample	5.76	5.73
Turkey Corn Root:		
Commercial sample of average cleanliness	4.37	4.528
Chionanthus:		
Select commercial sample	3.556	3.57
	3.80	3.50
Fraxinus, White Ash Bark:		
Select commercial sample	3.82	3.59
Centaury Herb, European:		
Clean commercial sample	4.42	4.51
Cocillana:		
Commercial sample of the powder	7.46	7.32
Para Coto:		
Select sample from Bolivia	1.121	1.106
Pulsatilla:		
Clean commercial sample	5.99	5.59

	Ash, per cent.	
Quebracho:		
Genuine bark from Aspidosperma Quebracho-blanco Schlechtendal	5.902	6.77
Rumex:		
A. Commercial sample powdered Rumex (Ash, very sandy, microscope showed much sand in the powdered drug.)	22.19	22.15
B. Commercial sample whole Rumex, select, very clean; powdered in this laboratory	4.73	4.4
C. Commercial sample whole Rumex, ordinary quality; powdered in this laboratory	7.7	7.9
D. Sample prepared from a plant of Rumex crispus grown, 1914, in the Medicinal Plant Garden, College of Pharmacy, University of Minnesota; powdered in this laboratory	3.03	2.89
E. Sample prepared from a plant of Rumex obtusifolius, grown, 1914, in Medicinal Plant Garden, College of Pharmacy, University of Minnesota; powdered in this laboratory	3.33	3.003

All of the above samples reported upon were purchased as the whole drug, unless otherwise stated. The authenticity of each was determined by pharmacognostical methods, and then a representative portion was powdered and incinerated in the usual way.

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University of Minnesota.

A COMPARISON OF THE VALUE OF VARIOUS FLAVORINGS FOR EMULSION OF COD-LIVER OIL.[1]

By GEORGE M. BERINGER, JR.

For some time the writer has surmised that a systematic study of this subject would yield many surprises. The results seem to justify that surmise.

A quantity of plain emulsion of cod-liver oil, U. S. P., without flavoring, was prepared. To separate portions of this were added all the commonly known volatile oils and aromatics of a pleasant flavor. These were used in the proportions of 4 c.c. per litre, except in the few cases otherwise noted. The samples thus prepared were arranged in the order of the value of the various flavors in disguising odor and

[1] Proc. N. J. Pharm. Assoc., 1914, p. 81.

taste. Of course, the placing of any individual sample in such a series would vary somewhat according to the personal taste of the observer. It is not thought, however, that the average observer would make a change in the position of any given sample of more than one or two numbers, so that such an arrangement would give a fair idea of the relative values of the flavors employed. The series thus arranged seemed naturally to divide itself into several fairly distinct groups.

In the first group came oils of coriander and geranium, which completely covered, *i.e.*, blended with or drowned, the fishy flavor of the cod-liver oil, so that it was not apparent to taste or smell. Oils of anise and cardamom (the latter in the proportion of 2 c.c. per litre), also in the same class, are almost equally valuable.

The second group consisted of oils of bitter almond, cloves, and pimenta, and, also, vanillin (1 Gm. per litre). These only partly covered the taste and odor of the cod-liver oil, but were very persistent and might prove of value blended with some of the flavors in the first group.

The third group contains oils of peppermint, spearmint, lemon, orange, and Ceylon cinnamon. These flavors stand out very strongly and almost completely mask the odor, *but not the fishy taste* of the cod-liver oil. In the latter respect they are distinctly inferior to those of the second group.

In the fourth group stand oils of caraway, cassia, sassafras, wintergreen, betula, and nutmeg. These flavorings seem actually to *accentuate* the fishy taste of the cod-liver oil! This is particularly noticeable in the cases of wintergreen and nutmeg. Wintergreen flavor comes out strongly both in taste and odor, but has no effect whatever in drowning the fishy taste.

Coumarin was tried in the proportion of 1 Gm. per litre, as it was thought it might have value as a blend, but the indications were very unfavorable.

A cacao emulsion of cod-liver oil has been recommended by a large manufacturer, with the statement that it is " entirely free from fishy taste and odor." This does not seem to be quite true, and it seems to the writer that what little disguise the preparation gives is due mostly to aromatics and substances other than cacao which it contains. A comparison of the samples with others of the series will show, it is believed, many better and simpler flavorings.

SOME REASONS WHY A PHARMACIST SHOULD MAKE HIS OWN PREPARATIONS.[1]

By JOHN F. MCANULTY, JR.

The question as to whether a pharmacist should make his own preparations or buy them already made, will probably always remain an open one.

There are many good arguments that can be advanced by either side, but, after all is said, the matter rests with the individual case. Beyond doubt, a pharmacist can make most of his own preparations more scientifically, and cheaper, than the big manufacturer. He does not, it is true, have the same facility to get up as artistic a package, but he has the advantage of being able to say he made it himself.

There is a good bit in the knowledge of every step, and ingredient used, in the manufacture of a preparation bearing your name. In fact, it clinches your selling arguments, for a customer instinctively knows when you are telling the truth about a preparation.

You may assert all you please about having the goods made for you under your own formula, but when your customer buys the same package with another man's name inserted at the bottom of the label, down the street, your talk is worse than useless. The confidence of the customer in you is killed forever.

The question of saving money also counts, as money saved is surely money earned.

Take a cough syrup like the White Pine Cough Syrup of the N. F. for instance. Most every pharmacist in this State uses a syrup of white pine during the winter months. Many buy their preparation already made under the transparent argument of being able to do it cheaper, without the trouble and bother to manufacture and bottle one of their own.

Do you know that you can make a syrup according to the N. F. formula for Syrupus Pini Strobi Compositus, bottle it in 3½-ounce bottles, label and put in a carton for five cents? Can a manufacturer guarantee you an N. F. syrup for any price near that?

This price will hold good for a small as well as large quantity of the syrup, and you have the assurance of selling a preparation that

[1] Proc. N. J. Pharm. Assoc., 1914, p. 52.

is standard, good, and therapeutically efficient. By adding a half ounce of syrup of tar to each bottle, you have a white pine and tar cough syrup that is sure to please.

Then there are corn remedies. The general demand seems to be for the green liquid preparations, and the Collodium Salicylatum Compositum N. F. fills this demand nicely. This can be dispensed in two-drachm vials having a brush or glass rod attached to the cork or stopper, at four or five cents a bottle. How does that compare with 75 cents per dozen in six-dozen quantities? This is the price you pay for an article that is not even N. F. This article sells generally for 15 cents, and thus yields a nice profit.

Cold cream is another preparation that can be made cheaper and better at your own store. For prescription use none but the U. S. P article should be dispensed. This keeps well if the ingredients, used in making it, are of good quality.

There is a demand for a cheaper cold cream, and one that will keep practically forever, under most any condition. The popular taste runs to the petroleum oil cold creams. A very good formula for such a cold cream is that of the U. S. P., Unguentum Aqua Rosæ, substituting white mineral oil for the sweet almond oil, and using the same method of manipulation.

Such a cold cream can be made for 17 or 20 cents per pound, as against a prominent manufacturer's price of 40 cents in five-pound quantities. You can make a single pound for 20 cents.

A nice jar can be bought, having a design and the words "Cold Cream" stamped on the lid, for about 3 cents for half-ounces, 5 cents for one-ounces, and 7 cents for two-ounces.

Therefore, an ounce package of cold cream made in this way costs about 6 cents and retails for 15 cents. You cannot buy as good a cold cream for less than 75 cents per dozen, and then the packages are short measure.

From the foregoing it is not hard to see where many dollars can be saved in the course of a year by the pharmacist making his own preparations.

There is always the additional satisfaction of being able to stand back of a preparation and say, "I made it and know it is good." The personal element counts for much in the drug business these days, and it is only by developing a good personality with your customers that the influence of the chain stores', machine-working clerks can be successfully combated.

THE PINEAL GLAND IN RELATION TO SOMATIC, SEXUAL AND MENTAL DEVELOPMENT.[1]

By CAREY PRATT MCCORD, M.D., Detroit.

From tumors involving the pineal gland, two distinct systems of symptoms and signs ensue, the neurologic and the metabolic. The neurologic manifestations arise from the encroachment of the neoplasm on the intracranial contents and are indications of changes in pressure, in placement and of destruction of tissue. Such changes are the consequence of pineal tumors at any age of the patient; but in pineal tumors appearing in prepuberal life a second group of changes arises, the metabolic. These metabolic alterations are referable to disturbance in the gland's secretory function. Apparently only in young males is this syndrome complete.[2] It consists of (1) early sexual development evidenced in the enlarged sex organs, pubic hair, general body hair, early changes in voice; (2) precocious mental development evidenced in the maturity of thought and speech, and (3) general body overgrowth to the extent that a child of 5 or 6 years may have the appearance of a child of 11 or 12.

A case reported by Machell[3] presents these changes in a striking manner. The patient was a boy less than six years old at the time of the publication. At the age of five months there was pubic hair, erections at seventeen months, emissions at thirty months. The patient's weight was 7½ pounds above normal at four months of age, 12 pounds in excess at 8 months, 20 pounds in excess at three years. When the patient was forty-four months old, his height was 8½ inches above normal for a child of that age. At forty-eight months the circumference of the head was over two inches in excess of normal. The voice was a deep bass. Mental precocity was very marked and the general bearing and language was that of a much older person.

[1] Read before the Section on Pathology and Physiology at the Sixty-Fifth Annual Session of the American Medical Association, Atlantic City, N. J., June, 1914. Reprinted from the *Jour. Amer. Med. Assoc.*, July 18, 1914, p. 232.

[2] For review of clinical cases see Bailey, Pearce, and Smith Ely Jelliffe: "Tumors of the Pineal Body," *Arch. Int. Med.*, December, 1911, p. 851. For Physiology and Anatomy, see Vincent Swale: "Internal Secretion and Ductless Glands," 1912.

[3] Abstract taken from *Medical Chronicle*, 1912, lvii, 154.

On account of the difficulties attending experimentation on this vestigial organ, the clinical findings with subsequent necropsy records have been the prime factor in the formulation of the prevailing ideas as to this gland's functions. The conception of this gland's function, however, has in part been developed from laboratory studies, notably from the results concomitant to the extirpation of the organ. This has been attempted frequently, but the situation of the gland is such that in the greater number of instances death followed the operative procedure, from hemorrhage or injury to the vermis or the occipital lobes. By operating on a large number of animals some workers have had a few animals survive. No changes attended the removal of the gland by Biedl,[4] Dandy,[5] and Exner and Boese,[6] but Foa,[7] ablating the gland in chicks, and Sarteschi [8] in young rabbits and puppies, report the production of the precocious macrogenitosomatic syndrome.

The publications growing out of these several clinical and laboratory studies have given rise to conceptions of this organ and its functions that may be thus epitomized:

The pineal body (epiphysis cerebri), probably the remains of a parietal eye, is situated just beneath the splenium of the corpus callosum, resting on the anterior quadrigeminate bodies, and is attached by its base to the habenular commissure. The gland varies in size, shape, and pigmentation, and does not stand in any proportional relation to the size of the brain or size of the body. The pineal body contains glandular elements, but these are few and not well defined. The greatest postnatal development is in the first years of life, and, so far as is known, the gland is only functionally active in the prepuberal life. On the assumption that tumors destroy the gland and deprive the body of the substances generated by it, the function of the gland is generally described as retarding and holding in abeyance too rapid development in childhood, of the body, mind, and sexual characteristics. When precocity in development appears in conjunction with pineal tumors, it is attributed to lack of glandular secretion.

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[4] Biedl: "Innere Sekretion," 1910.

[5] Dandy, cited by Cushing: "Pituitary Gland and Its Disorders," p. 283.

[6] Exner and Boese: *Deutsch. Ztschr. f. Chir.*, 1910, cvii, 182.

[7] Foa: *Arch. Ital. de Biol.*, 1912, lvii, 233.

[8] Sarteschi: "Pathologia," 1913, p. 707.

Below are recorded some findings from experimental work that are entirely in accord with the results obtained by Dana and Berkeley.[9] Contrary to the view that precocious development is due to pineal deficiency (hypopinealism), the same precocity in development has been brought about by the oral administration of pineal gland tissue.

Experimental Data.

The general plan of work entailed in this study has been to feed to very young animals minute quantities of pineal tissue and to record the weight changes, sexual differences, and, in the case of dogs, increased mentality, over control animals maintained under otherwise identical conditions. One hundred and ten guinea-pigs, eighteen puppies, fourteen adult dogs, and sixteen chicks have been under observation.

Fresh pineal glands from cattle have been employed. These were in part from veal, in part from young adults approximating three years, and in part from the general run of cattle from the abattoirs. The glands averaged in weight (on weighing sixty glands) 2.14 grains. There were in the many thousand glands making up the several pounds that have been used marked variations in size, shape, and melanopigment. This pigment, which was present in a high percentage of glands, involves chiefly the encapsulating tissue.

For feeding experiments the glands were prepared for permanent use in the following manner: The fresh glands were rinsed free of blood and stripped of adherent tissue. They were ground to a fine paste in the Latapie grinder, and, without drying, the paste was admixed with milk-sugar in such quantity that ½-grain milk-sugar represented 10 mg. pineal tissue. The mass was made into ½-grain tablets and quickly dried at room temperature.

Early in the work it was apparent that the more striking results were being obtained from the animals fed with pineal substance from cattle not having reached adult life. Efforts were then made to establish quantitatively the activity and the identity of the various experimental lots of pineal preparations by employing the methods commonly used in testing the activity of endocrinous derivatives. Although certain cardiovascular changes regularly follow the intravenous administration of pineal extracts to dogs, the extent of these changes is not a measure of the activity of the gland as a stimulator of growth.

[9] Dana and Berkeley: *Med. Rec.*, New York, 1913, lxxxiii, 835.

On the hypothesis that precocious development is due to hypopinealism, the first work was done in anticipation that feeding would retard development and prolong the presexual life. This was begun on two chicks incubated in the laboratory. Beginning at the age of

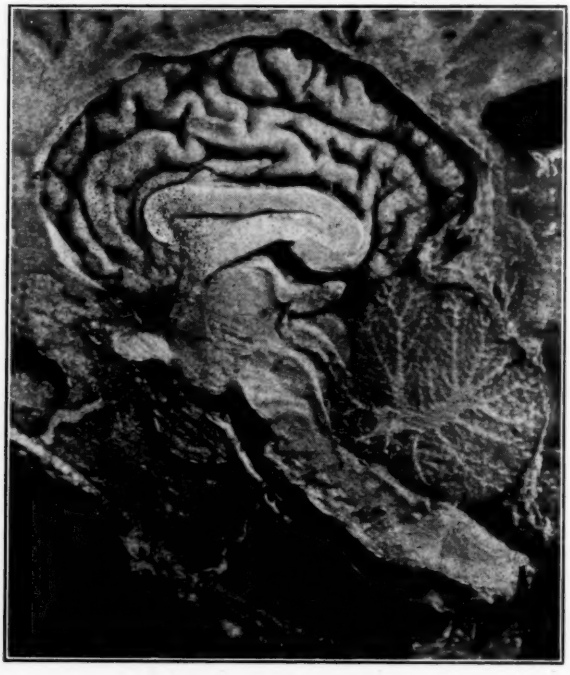

FIG. 1.—Position, relations and relative size of the pineal gland. Taken from beef 3 years of age.

two days, one was fed 10 mg. veal pineal tissue, three times weekly, the other (and in all cases of controls) was fed a blank tablet of milk-sugar. The difference in growth should be noted (Table I).

TABLE I.

Results of Feeding Pineal Gland to Chicks.

	Third week, grammes	Sixth week, grammes	Ninth week, grammes	Twelfth week. grammes
Pineal	219.5	557.7	895	925
Control	92.5	286.5	550	700
Difference	127.0	271.2	345	225

The striking disproportion in size and the marked skeletal overgrowth, making the large chick very awkward in his movements, soon made these chicks a laboratory curiosity, but the small number and the different sex did not justify any inference as to the influence of the pineal feeding. The results, however, were so striking that at once work was instituted in a more extensive way.

A lot of fifty guinea-pigs in the second week of life was selected and divided into test and control groups. The test pigs were fed daily 10 mg. veal pineal tissue. The controls were fed a ½-grain milk-sugar tablet. Other conditions for the two lots were identical. The results obtained are given in Table II.

TABLE II.

Results of Feeding Pineal Gland to Young Guinea-Pigs.

Control, 25 pigs Average initial weight, 201.2 grammes Age, 2 weeks			Pineal, 25 pigs Average initial weight, 204.3 grammes Age, 2 weeks		
Weeks	Average weight, grammes	Gain, grammes	Weeks	Average weight, grammes	Gain, grammes
1	198.7	—2.5	1	213.2	8.9
2	220	21.3	2	236.8	23.6
3	226.8	6.8	3	247.6	10.8
4	251	24.2	4	273.2	25.6
5	265.3	14.3	5	299.9	26.7
6	265.7	0.4	6	311.1	11.2
7	292.2	26.5	7	338	26.9
8	306	13.8	8	361.4	23.4
9	316.3	10.8	9	365.5	4.1
10	356.5	40.3	10	410.8	45.3

	Grammes		Grammes
Average weight at end of tenth week	356.6	Average weight at end of tenth week	410.8
Average initial weight	201.2	Average initial weight	204.3
Average gain	155.4	Average gain	206.5
Gain, per cent	77.0	Gain, per cent	100.0

Excess gain of pineals over controls, 23 per cent.

This excess in weight of pineal-fed guinea-pigs over their controls is a symmetrical overgrowth. There is some increased adipose tissue, but this is generally distributed and not localized in any one region of the body. At no time has it been possible to continue this excessive growth above the normal adult size. As the animals approach adult size the pineal feeding is less effective and after full maturity is attained is without effect. There has been no tendency to gigantism.

As a step toward determining the metabolic differences, quantitative urinalyses were made on twenty-four-hour composite samples of urine from the two groups.[10] With proper regard for the numerous other factors that might vitiate the results obtained from urinalyses, there is a suggestive difference in the two urines as may be seen in the summary given in Table III.

TABLE III.
Summary of Analysis of Urines.

	Pineal	Control
Total volume collected (24 hours)	187 c.c.	160 c.c.
Specific gravity (15.5 C.)	1.016	1.019
	Per cent.	Per cent.
Total solids	2.51	3.02
Water	97.49	96.98
Total mineral matter	1.21	1.37
Total nitrogen	0.628	0.872
Total creatinin	0.018	0.025
Phosphoric acid (as P_2O_5)	0.065	0.043
Calcium	0.016	0.018
Magnesium	0.020	0.018
Alkalinity (as Na_2CO_3)	0.053	0.037

Chicks.—A lot of fourteen chicks was secured at the age of one week. At so early an age sex could not be determined, and the lot was divided into test and control groups without knowledge as to grouping by sex. The test chicks were placed on veal pineal tissue for one week, with a resultant greater growth than controls. For the next four weeks they were fed pineal tissue from old cattle, without gaining. On being placed on the original veal preparation the test chicks again grew in excess over controls.

Dogs.—The eighteen dogs employed represent four litters. Infection of these puppies with distemper interfered seriously with the weight charts of these animals. So long as infections could be kept out of the animal quarters, the test animal outgrew the controls, but the wasting from infections interfered seriously with average results over prolonged periods. It was in connection with puppies that some differences in intelligence were observed. No great import is attached to these observations, but it was noted that the pineal-fed dogs were about one month ahead of the others in their habits. They were the first to learn to lap milk, the first to respond to a call, the first to be able to find their way back to the kennel. When work on

[10] I am under obligations to Mr. Lewis Davis for these analyses.

these animals was discontinued, only the pineal-fed animals were in demand as pets, and those choosing them did so without any knowledge as to the differences in feeding. Of much more importance as regards increased intelligence are the favorable results reported by Berkeley,[11] who administered pineal tissue to mentally defective children and performed Binet tests as a criterion of mental advancement.

Precocious Sexual Development.—A group of forty-eight guinea-pigs was divided into test and control lots. There was an equal number of males and females in each lot, but the males and females were separated. The test pigs were fed veal pineal tissue in 10-mg.

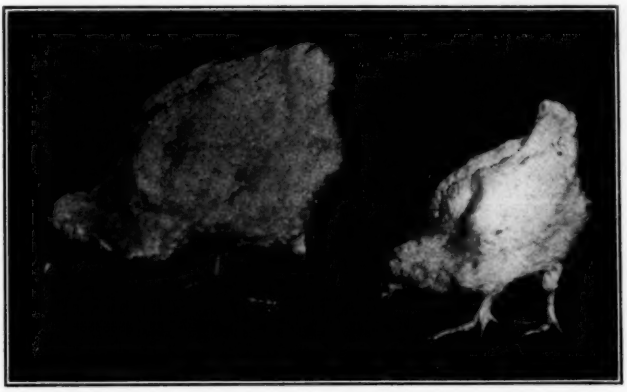

FIG. 2.—Effect on growth of feeding pineal-gland tissue to chicks. The larger chick was fed 10 mg. pineal tissue three times weekly.

amounts daily. Feeding was begun when the animals were two weeks old and continued for nine weeks. The males and females of each group were then placed together in breeding-pens. As a measure of any difference in sexual development it was thought desirable to note the date of birth of young in the two lots. As the end of the approximate gestation period approached, these animals were observed as to the date of giving birth to young. All except two of the pineal-fed pigs gave birth to young before the first of the controls.[12]

[11] Berkeley: *Med. Rec.*, New York, 1914, lxxxv, 85, 513.

[12] In a second series of fifty guinea-pigs observed as to sexual differences, the males and females have been kept together from birth. Some of the females to whom pineal gland tissue has been fed have already given birth to young and many others are within the last ten days of gestation. With the exception of one pig, the control animals evince no signs of pregnancy.

Fourteen days elapsed between the birth of young of the first pineal-fed pig and the first control pig. In all cases the young were normal and in no wise different from any other young pigs.

Comment and Summary.

In the foregoing records of experiments it may be observed that some of the changes generally attributed to deficiency of pineal secretion may be produced by supplying an added amount of pineal substance. In an effort to reduce to rationality these identical findings derived from two opposing sources, the so-called destructive neoplasms of the pineal gland on the one hand, and the feeding of the gland on the other, there arise two possibilities: First, this syndrome may appear from disrupting the general endocrinous balance from either increasing or decreasing the amount of pineal secretion avail-

Fig. 3.—Effect on growth of guinea-pigs produced by feeding pineal-gland tissue. Control pigs to left, test pigs to right.

able for the body's use. These secondary changes in the other endocrinous glands are now in the course of investigation. Second, the cells of the neoplasms involving the pineal gland may retain some of the metabolic and other functional characteristics of the normal pineal cell from which they were derived, and the peculiar body, sexual and mental changes in patients with such tumors are all manifestations of increased rather than decreased pineal activity. One of the most frequently occurring lesions of the pineal is the adenoma, and there is abundant evidence that at times cells of adenoma functionate after the manner of the cells from which they arise. In adenoma of the liver in cases reported by Weber,[13] Rolleston,[14] Wheeler,[15] and Ribbert,[16] distinct bile secretion by tumor-cells has been pointed out.

[13] Weber: *Proc. Roy. Soc. Med.* (Path. Sec.), 1910, iii, 147.
[14] Rolleston: "Diseases of the Liver," 1905.
[15] Wheeler: *Guy's Hosp. Rep.*, 1909, lxiii, 225.
[16] Ribbert: *Deutsch med. Wchnschr.*, 1909, xxxv, 1607.

Ribbert established that the bile present in such tumors was not the bile of icterus from necrotic liver-tissue by demonstrating that the scirrhous encapsulating tissue was free from bile-stain and that the bile was confined to the liver-like cells of the active tumor. In at least one case, a metastasis in the lung from the liver secreted bile. In this connection it is significant that the functionating glandular cells of typical thyroid structure have been found in thyroid metastases in bone-tissue. Furthermore, in myeloma of the bone-marrow the cytoplasm [17] of the tumor-cells contains the granules that characterize normal myelocytes; that is, the tumor to a certain extent assumes the function of the bone-marrow. All considered, it is perceived that functional activity of tumor-cells is *not* infrequent. Germane to the present contention is the statement by Hinds Howell [18] in describing the characteristics of the cells of the pineal tumors of his three cases. He says:

"A noteworthy feature is the similarity of these tumor-cells in many instances to those of the normal pineal gland."

The results of this work lead me to the conclusion that the administration of minute quantities of pineal tisue from young animals to young animals stimulates rapid growth of the body, but not beyond normal size; also, there are less well-established indications of precocity of mental and sexual development.

BACTERIAL *VERSUS* VEGETABLE TOXINS.*

By J. Stanley White, Ph.C.

In these days, when the values of such products as antidiphtheria serum and antitetanus serum are recognized on all sides as being unique in their respective spheres, it is interesting to recall that it was as the result of the study of a product obtained from a purely vegetable source that these biological products assumed a practical form. The substance referred to is ricin, the toxalbuminoid principle found in castor-oil seeds, and a comparison of this and allied substances,

[17] Weber and Ledingham: *Proc. Roy. Soc. Med.* (Path. Sec.), 1909, ii, 206.

[18] Howell, Hinds: *Proc. Roy. Soc. Med.* (Neurolog. Sec.), 1910, iii, 65.

* Reprinted from the *Pharmaceutical Journal and Pharmacist*, Feb. 6, 1915, p. 156.

both of vegetable and animal origin, with similar products elaborated by bacteria may not be without interest.

It is only comparatively recently that the existence of poisonous proteids or toxalbumins has been recognized. The idea that a proteid can produce dangerous or even fatal symptoms or act in any way except as a food dates only from 1884, but, according to Cushny, most of the animal poisons are now believed to be of proteid nature, and the toxins formed by microörganisms of disease are almost certainly of the same class.

The most important toxins or toxalbumins of the vegetable kingdom are ricin, abrin, and crotin. The two latter are obtained respectively from the seeds of *Abrus precatorius* (jequirity) and *Croton Tiglium,* but they closely resemble ricin, and it will only be necessary here to refer at any length to this last-named substance.

Ricin is an intensely poisonous phytoalbuminose, which may be obtained from castor-oil seeds after the removal of the oil. It occurs only in the endosperm and embryo, where it is present to the extent of 2.8 to 3 per cent., and may be obtained from fresh decorticated and strongly expressed seed by percolation with a 10 per cent. saline solution in which it is soluble. The percolate is filtered and saturated at 20° to 22° C. with magnesium sulphate, and the resulting white precipitate separated from the crystallized salts by dialysis. This preparation is not pure ricin, and probably contains a large proportion of albumins. As thus obtained, ricin is a white, odorless, strongly toxic, ash-yielding powder, insoluble in alcohol, ether, and chloroform.

The chemical nature of ricin appears to be analogous to that usually ascribed at the present time to the bacterial toxins and ferments and the name toxalbumin, originally suggested by Kobert and Stillmark, who first investigated the substance, is abandoned. Ricin differs in a marked manner from the bacterial toxins and snake venoms by its relative stability towards the natural fluids and ferments of the alimentary tract. For this reason it appears to be absorbed by the intact alimentary tract, and thus may act as a poison when administered by the mouth. The action of ricin is, however, much less powerful in the stomach than when injected hypodermically. The toxicity of the substance is enormous, and it may certainly be regarded as among the most powerful vegetable poisons when injected directly into the blood.

According to Ehrlich, 1–2000th grain per 2 pounds body weight is fatal; 1 Gm. (15.43 grains) subcutaneously is sufficient to kill one

and a half million guinea-pigs, while the lethal dose for man is supposed to be 0.30 Gm. by the mouth or 0.003 Gm. subcutaneously. It should, of course, be remembered that these figures do not refer to pure ricin, but to ricin contaminated with more or less albumin. Smaller doses, injected hypodermically, soon produce immunity, antiricin being formed.

As previously stated, the observation of Ehrlich of this protective reaction laid the foundation of serum therapeutics. Before discussing the production of antiricin it may be as well to briefly consider the toxins elaborated by bacteria. When pathogenic bacteria grow and multiply in the body, symptoms of poisoning (toxæmia) are manifested; consequently it was inferred that bacteria either produced poisons during their growth or contained poisons. Subsequent experiments proved that the poisonous effects of a few bacteria which passed out into the surrounding media, and the poisonous effects of the other class, seemed to be due to the actual constituents of the bacterial cells. The former are termed exotoxins or extracellular toxins, and the latter endotoxins or intracellular toxins. Some bacteria, on the other hand, notably the tubercle bacillus, elaborate both exotoxins and endotoxins. These toxins are substances of a very complex composition, probably allied to the proteins. In some instances they appear to be of the nature of enzymes or ferments, and they are direct products of the bacterial cells.

Among the few bacteria producing extracellular toxins or exotoxins the bacillus of diphtheria and the bacillus of tetanus are the most important. They are extremely poisonous; in fact, it has been computed that the toxin elaborated by a virulent culture of the bacillus tetanus is the most potent poison known to science to-day. These exotoxins being excreted by the bacteria, are found in solution in the liquid culture media containing the growing microörganisms. Serum from an animal immunized by injecting into its body small and increasing doses of these soluble toxins, administered at regular intervals and given over a long period of time, is rich in antitoxin. This antitoxin, when properly prepared and standardized, constitutes the antitoxin of commerce. Diphtheria and tetanus antitoxins are prepared in this manner.

In the case of the bacteria which do not secrete a soluble toxin, the killed bacteria themselves are used for immunization. They constitute what are known as the antimicrobial serums, a familiar example of which is antistreptococcus serum, and should be distin-

guished from antidiphtheria and antitetanus serums, which are strictly antitoxic in nature.

Antiricin may be produced in exactly the same way as an antitoxin; in fact, antiricin might be described as a vegetable antitoxin. Rabbits have been immunized by gradually increasing doses of ricin until they have obtained an immunity of 5000, or, in other words, have developed so much antiricin in their blood-serum that they are not affected by 5000 times as much ricin as would have killed them had no preliminary treatment been instituted.

The immunity acquired for both ricin and bacterial toxins is entirely different from the tolerance acquired for morphine and other drugs. According to Cushny, the latter is due to the cells of the body becoming accustomed to being constantly bathed in a fluid containing the alkaloid. The same tolerance is acquired by various marine animals, which would be killed if suddenly changed to fresh water, but which are gradually acclimatized if the change is made more gradually by adding increasing proportions of fresh water to the sea water of the aquarium. In the case of ricin and bacterial toxins the immunity is due to formation in the body of a substance which antagonizes the original poison and constitutes what is known as an antitoxin. This antagonistic substance circulates in the blood, and can be withdrawn from the immune animal and injected into a second, which then acquires a certain degree of immunity, although less than that of the first. Just as diphtheria antitoxin and tetanus antitoxin are antagonistic only to their respective toxins, so also antiricin is antagonistic only to ricin and does not protect an animal from any other form of toxin.

Various animal poisons, such as snake venom, spider toxin, and eel serum, have been found to act in a similar manner, although, apart from bacterial toxins, snake venom is the only one used for therapeutic purposes. By means of this an antitoxin has been produced which has marked prophylactic properties against snake bites, and is used extensively in countries where poisonous snakes abound. In addition to the vegetable toxins—ricin, abrin, and crotin—toxins have also been obtained from poisonous mushrooms.

While antiricin has no practical therapeutic value, yet it was as the result of the study of this remarkably interesting substance that Ehrlich arrived at a practical method of standardizing the bacterial antitoxins, thus establishing a definite antitoxin unit value for these products.

It is not within the province of this article to discuss the physiological methods employed in standardization or the ingenious side-chain theory which Ehrlich evolved to explain the probable action of the antitoxins in producing immunity. Suffice to say that the discovery of ricin paved the way for some of the most wonderful products used in medicine to-day. It is only necessary to consider the tremendous number of lives which have been saved by the timely use of antidiphtheria serum, and particularly antitetanus serum in the present campaign, to fully appreciate its importance.

A SYNOPSIS OF H. R. NO. 6282.[1]

An act to provide for the registration of, with collectors of internal revenue, and to impose a special tax upon all persons who produce, import, manufacture, compound, deal in, dispense, sell, distribute, or give away opium or coca leaves, their salts, derivatives, or preparations, and for other purposes.

Commonly known as THE HARRISON BILL.

And Internal-Revenue Regulations No. 35 for its enforcement. *In effect March 1, 1915.*

An act of especial interest to physicians, pharmacists, veterinarians, dentists, and all who have occasion to possess, sell, dispense, or to prescribe such medicines.

HISTORICAL.

The United States, through its delegates appointed by the Department of State, has taken an active interest in the several International Conferences that have been held at Shanghai, China, and at The Hague for the purpose of suppressing improper traffic in habit-forming drugs. These delegates committed the American nation to the adoption of legislation that would eradicate this evil in the United States and demonstrate the earnestness and sincerity of the American people in this international movement.

In a special message to Congress in 1910, President Taft advocated a national law directed against this evil and based on the power granted by the Constitution to Congress to control interstate commerce. Dr. Hamilton Wright, who had been a delegate from the United States to these conferences, was likewise very zealous and energetic in his demands for a stringent federal anti-narcotic law.

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[1] Prepared by George M. Beringer, A.M., Ph.M., Camden, N. J.

In 1912, Francis Burton Harrison, Representative from New York, introduced in the Sixty-second Congress the first draft of his anti-narcotic bill and, since that time, his name has been associated with the proposed legislation. The measure has since been largely rewritten and remodelled mainly through the efforts of the National Drug Trade Conference. It was reintroduced in the Sixty-third Congress, and the agitation for a National Anti-Narcotic law culminated in the final passage of the act by Congress on December 10 and the approval by President Wilson on December 17. The act as passed is based upon the constitutional right of Congress to impose taxes.

SECTION 1.—Requires that on and after March 1, 1915, every person,[2] who produces, imports, manufactures, compounds, deals in, dispenses, sells, distributes or gives away opium or coca leaves or any compound, manufacture, salt, derivative or preparation thereof, must register[3] with the collector of internal revenue and pay a special tax of $1 per annum.

Exemptions—

(*a*) Employees of persons registered under the act, when acting within the scope of such employment.

(*b*) Officers of U. S. Government service in purchasing said drugs for the government service.

(*c*) Officers of the State, county, or municipality making purchases of said drugs for State, county, or municipal hospitals or prisons.[4]

SEC. 2.—Makes it unlawful to sell, barter, exchange, or give away any of the said drugs, except on the written order of a person registered under the act and on an official order form.[5] The person filling such an order must file it according to its registry number and district

[2] "Person" means a partnership, association, company, or corporation as well as an individual.

[3] Registration must be made on the official form supplied by the collector. If the "applicant" is engaged in more than one profession or business where any of said drugs are made, stored, or dispensed, a separate registry must be made, and a special tax paid for each such profession or business.

[4] Sanitariums, hospitals, dispensaries, etc., that are not owned by the U. S. Government, or by State, county, or municipality, must register and pay the special tax or they cannot legally have in possession, purchase, or dispense said drugs.

[5] Requisition must be made to the Internal Revenue Collector for these forms, which are issued only to persons registered, in books of 10; 10 cents is the charge for each book.

and preserve it for two years, subject to the inspection of authorized officers of the Government of the United States, the State, county, or municipality. The person issuing [6] such an order must preserve a duplicate on the official order form stub for two years and subject to the same inspection.

Exemptions—

(*a*) Dispensing by a physician, dentist, or veterinary surgeon registered [7] under the act, in the course of his professional practice only. A record must be made and kept, subject to inspection, for two years, of the drugs, amount, date, name, and address of the patient; exception is made as to the record of such drugs as he may dispense to a patient he shall personally visit.

(*b*) Dispensing by a dealer upon the written prescription of a physician, dentist, or veterinary surgeon registered under the act. The prescription must be signed and dated by the prescriber, and must have thereon his registry number, the location of his office, the name and address of the patient.[8] All such prescriptions must be filed, so as to be readily accessible for inspection, and preserved for two years.[9]

Refilling of prescriptions containing the said drugs in larger amount than

2 grains of opium,
¼ grain of morphine,
⅛ grain of heroin,
1 grain of codeine,

or any salt or derivative of any of them in one fluidounce, or, if a solid or semi-solid preparation, in one avoirdupois ounce, is prohibited.[10]

[6] These order forms can be used only by the person whose registry number and name is stamped thereon by the revenue office.

[7] Physicians, dentists, and veterinary surgeons are not exempted from registration. Unless registered they cannot have possession of, purchase, prescribe, dispense, or give away any of the said drugs.

[8] The regulations provide that druggists must refuse to fill any such prescription unless signed as required, nor must a prescription for said drugs be filled by a druggist if he has reason to suspect that it is fraudulently issued or obtained.

[9] A separate file should be kept for such prescriptions, otherwise a record must be kept showing the file number, the name of the prescriber and the person for whom the prescription is filled.

[10] Prescriptions containing coca leaves, cocaine, eucaine, or any of the derivatives or synthetic substitutes for these cannot be refilled.

(*c*) Drugs shipped to a foreign country in accordance with regulations prescribed by that country.

(*d*) Sales to the officers exempted in Section 1.

SEC. 3.—Authorizes the collector of the district to call upon any person registered under the act for a report, verified by oath, setting forth the quantity of the said drugs received by him during a period immediately preceding the demand, not exceeding three months. The report must state in detail the dates and from whom received, drugs and quantity.[11]

Every person dispensing directly[12] to the consumer any of said drugs must on the first day of March, 1915, prepare and keep on file an inventory of all such drugs, preparations or remedies so held and such inventory must be verified by oath not later than the fifth day of March, 1915.

Preparations exempted under Section 6 from the provisions of this act need not be included in such inventory.

SEC. 4.—Makes it unlawful for any person not registered under the act to send, ship, carry, or deliver any of the said drugs in interstate commerce. Common carriers and employees of registered persons acting within the scope of such employment, messengers delivering prescriptions, and the officers exempted under Section 1 are exempted from provisions of this section.

SEC. 5.—Determines the right of inspection[13] of records and reports made in accordance with the provisions of this act, by officers of the Treasury Department, and officials of the State, county, or municipality who are charged with the enforcement of laws regulating the traffic in said drugs.

SEC. 6.—Exempts from the provision of the act preparations and remedies which do not contain more than

2 grains of opium,
¼ grain of morphine,
⅛ grain of heroin,
1 grain of codeine.

[11] Official forms for such requests and reports are provided by the department.

[12] Dispensing druggists, physicians, dentists, veterinary surgeons, and dispensaries are such direct dispensers.

[13] Under authority of Section 10, inspectors will be appointed to visit at irreguar intervals and make inspection of records, orders, prescriptions, reports, etc. Investigations are to be conducted so as not to unnecessarily annoy or interfere with business.

or any salt or derivative of any of them in one fluidounce, or, if a solid or semi-solid preparation, in one avoirdupois ounce; or to liniments, ointments, or other preparations which are prepared for external use only, except liniments, ointments, and other preparations which contain cocaine or any of its salts or alpha or beta-eucaine or any of their salts or any synthetic substitute for them; provided, that such remedies and preparations are sold, distributed, given away, dispensed, or possessed as medicines and not for the purpose of evading the intentions and provisions of this act.[14]

Decocainized coca leaves and preparations made therefrom are likewise exempted.

SEC. 7.—Extends the statutes relating to internal revenue taxes so as to be applicable to this act.

SEC. 8.—Makes it unlawful for any person not registered under this act to have possession or control of any of the said drugs unless same has been prescribed in good faith by a physician, dentist, or veterinary surgeon registered under the act.

Further exemption is provided for an employee of a registered person who has possession by virtue of his employment and not on his own account, officers exempted under Section 1, warehouseman holding possession for a person registered, common carrier engaged in transporting such drugs.

A nurse is permitted to have any of said drugs when under the supervision of a physician, dentist or veterinary surgeon registered under the act, and having possession by virtue of such employment and not on his or her own account.

SEC. 9.—Fixes as penalties for violation or failure to comply with the requirements of the act a fine of not more than $2000 or imprisonment of not more than five years, or both, in the discretion of the court.

SEC. 10.—Authorizes the appointment of Revenue Department employees to enforce the provisions of the act.

SEC. 11.—Appropriates $150,000 for the purpose of carrying into effect the provisions of the act.

SEC. 12.—Provides that this act is not to invalidate the Federal Food and Drugs Act or the act to prohibit the importation of and use of opium for other than medicinal purposes.

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[14] Compliance with the provisions of the Harrison Bill does not relieve any person from strict observance of the State laws or municipal ordinances regulating the sale of narcotics.

DRUG INTOXICATION.[1]

An Economic Waste and a Menace to Public Health.

By M. I. Wilbert, Technical Assistant, Division of Pharmacology, Hygienic Laboratory, United States Public Health Service.

It has been estimated that more than 200,000 persons die annually in the United States from so-called degenerative diseases, and the mortality statistics compiled by the Census Bureau show that in the registration area there has been an increase of more than 100 per cent. in the deaths from diseases of the kidneys, heart, and blood-vessels during the past thirty years.

While it is to be expected that the gradual decrease in the general mortality rate, particularly the decrease in deaths from readily preventable diseases like typhoid fever and smallpox, would tend to lengthen the average human life, and thus add to the number of deaths from these so-called degenerative diseases in advanced years, mortality statistics show that the greater proportion of the increase in the death-rate from diseases of the kidneys, heart, and blood-vessels has been among persons who should be and are generally considered to be in the prime of life. This great increase in the mortality of persons between forty and sixty years of age, from diseases characteristic of senility, constitutes a deplorable and unnecessary economic loss that is well deserving of careful and comprehensive study.

For many years it has been accepted as fact that changes in the natural resistance of the human body may be and are brought about by intoxications such as are produced by alcohol, tobacco, narcotic drugs, and the various occupational poisonings that are attracting such widespread attention at the present time. These several sources of intoxication have, however, long been recognized and considerable attention, time, and thought have been devoted to the study of their possible untoward effects. Their harmfulness was generally well known and some effort made to combat their influence even before the end of the eighth decade of the previous century, from which period the steady and somewhat rapid rise in mortality from degenerative diseases appears to date.

An important source of intoxication to which altogether too little attention has as yet been given is suggested by a comparative study

[1] Reprint from the *Public Health Reports*, vol. 29, No. 42, Oct. 16, 1914.

of the statistics published in the Thirteenth Census of the United States, in connection with the remarkable increase in the manufacture and inferentially, therefore, in the consumption of materials used as medicines. The paragraph relating to patent medicines and compounds and druggists' preparations shows that during the sixty years for which figures are obtainable the values of products of this type at the manufacturing establishment increased from $3,863,815 in 1849 to $141,941,602 in 1909. An even more impressive suggestion is presented by the appended table showing the increase in the number of establishments engaged in the manufacture of commodities of this type, the cost of the materials used, and the value of the products at the manufacturing establishment, compared with the increase in population of the United States during practically the same period of time.

*Number of Establishments Engaged in the Manufacture of Patent Medicines and Druggists' Preparations, the Cost of Materials Used and the Value of the Product as Manufactured Compared with the Population of the United States, Exclusive of Outlying Possessions, during the Corresponding Period.**

Year	Number of establishments	Cost of material	Value of product	Population of United States	Year of census
1909	3,642	$50,375,665	$141,941,602	91,972,266	1910
1899	2,154	31,949,890	88,790,774	75,994,575	1900
1889	3,089	15,571,187	43,940,120	62,947,714	1890
1879	620	7,906,138	16,885,498	50,155,783	1880

* Thirteenth Census of the United States, 1910, v. 8, pp. 451–452, and v. 1, p. 126.

Thus it appears that while the increase in population of the United States from 1880 to 1910 was approximately 83.3 per cent., the increase in the value of patent medicines and related products was 740.5 per cent. In other words, while the population of the United States was less than doubled, the value of the medicines manufactured and consumed was increased ninefold. The cost of the material to the manufacturer was seven times greater in 1909 than in 1879, and the value added by manufacture was eleven times greater in 1909 than it was in 1879. These figures, given above, high as they are, represent but a minor portion of the expenditures by American people for medicines of various kinds. Many, if not all, of the chemicals used as medicines are made in manufacturing establishments other than those included in the above enumeration, and other materials, particularly crude drugs and the finer grades of chemicals, are imported from

foreign countries. The table of imports for consumption in the United States for 1913 includes drugs, chemicals, and other products used as medicine to the value of more than $100,000,000. It has been conservatively estimated that the people of the United States expend annually upward of $500,000,000 for medicine, and that by far the greater bulk of the medicine purchased is consumed haphazardly and not under the direct supervision of experts whose knowledge would tend to prevent harmful intoxication and untoward results from the ingestion of potent and in many instances dangerously harmful preparations.

The relative quantities of some of the products imported are shown in the appended tables, compiled from the list of imported merchandise entered for consumption in the United States, issued by the Department of Commerce. The first of these tables shows the number of pounds of some of the more widely used botanical drugs imported into the United States during the years 1909 to 1913, inclusive, and the second table reflects the quantities of some of the more widely used medicinal chemicals entered for consumption during the same period.

When one considers the potential possibilities for harm inherent in practically all drugs and preparations it is astonishing that attention has not earlier been directed to the need for careful, systematic study of the possible untoward influences of the several drugs used.

The frequent, excessive or long-continued use of any one of a number of inorganic compounds, particularly the soluble salts of mercury, lead, uranium and related metals, has been shown to be irritating to the kidneys and capable of producing chronic lesions. The constant ingestion of many of the otherwise innocuous inorganic salts when contaminated by traces of arsenic or lead may, and undoubtedly will, produce toxic manifestations.

Many organic compounds have also been found to produce marked changes or secondary manifestations. The changes produced by alcohol and the narcotic drugs have been fairly well recognized and considerable data are also available regarding the harmful effects of the coal-tar analgesics, the several hypnotics, and a number of aldehydes and related products.

All of the important or active medicaments must of necessity have harmful influences when taken indiscriminately or for a continued length of time. It has been very properly asserted that the activity of drugs may vary to an infinite number of degrees. It may be

accepted as fact that whenever the activity is sufficient to produce a decided therapeutic effect in disease it is also sufficient to produce a deleterious effect when improperly used, either as to time or quantity. In other words, useful drugs are of necessity poisonous substances which tend to derange normal processes of the human organism and many of them must of necessity be extremely injurious to the various organs of the body if used at all liberally for any appreciable length of time.

Quantities of Some of the More Widely Used Botanical Drugs Imported into the United States during the Years 1909 to 1913, Inclusive.

	1909	1910	1911	1912	1913
	Pounds	*Pounds*	*Pounds*	*Pounds*	*Pounds*
Aloes	671,257	944,007	980,205	666,229	909,279
Asafœtida	42,335	95,536	114,686	138,066	134,579
Balsam of Peru	25,843	50,363	37,910	47,862	48,996
Benzoin	69,146	55,634	98,366	94,733	105,967
Buchu	.....	130,644	106,345	181,121	105,310
Cinchona	3,502,385	3,305,894	4,136,354	2,935,350	3,329,973
Copaiba	234,257	208,566	191,154	159,172	206,447
Cubebs	87,050	104,713	129,014	111,357	166,307
Gentian	1,485,389	1,177,433	1,537,919	1,585,612	1,796,928
Ipecac	35,166	36,261	27,654	41,627	54,648
Jalap	66,096	199,905	230,679	119,211	277,275
Nux vomica	1,666,957	2,738,662	4,330,402	2,427,187	2,306,735
Sarsaparilla	570,124	560,858	379,091	452,917	301,308
Senna	2,159,553	2,564,452	3,063,275	3,164,003	2,634,117

Quantities of Some of the More Widely Used Medicinal Chemicals Entered for Consumption in the United States during the Years 1909 to 1913, Inclusive.

	1909	1910	1911	1912	1913
Acid:	*Pounds*	*Pounds*	*Pounds*	*Pounds*	*Pounds*
Benzoic	491,739	364,650	502,878	470,004	863,015
Boracic	230,968	416,842	343,094	276,496	362,400
Carbolic	4,729,552	4,507,693	4,371,014	5,686,704	8,345,631
Citric	243,010	142,001	97,847	67,332	8,677
Salicylic	1,988	64,531	32,876	28,769	31,844
Tartaric	124,774	104,457	331,538	105,311	78,942
Aniline oil	1,950,620	1,946,805	1,917,202	1,843,443	2,015,318
Aniline salts	6,130,517	5,870,905	5,133,723	4,831,075	4,976,108
Caffeine	149,599	60,463	57,025	43,859	59,773
Camphor	2,421,023	3,519,233	4,218,430	2,404,140	3,941,170
Cinchona bark alkaloids	*2,330,304	*3,012,196	*3,102,194	*3,044,238	*3,237,994
Iodine	12,961	771,090	210,467	497,823	351,296
Lime, citrate of	3,917,274	4,114,256	5,219,544	5,903,501	5,526,954
Tartar and cream of tartar	32,121,394	28,415,045	29,312,257	23,746,330	29,548,388

* Ounces.

Quinine, for instance, the alkaloid of cinchona bark, is still used in rather large quantities and as such or in the form of bark was imported into the United States, in 1913, to the total of 2,065,000,000 average doses; enough to give every man, woman, and child from twenty-five to thirty doses each year. This drug has long been known to produce a characteristic form of intoxication accompanied by roaring in the ears, impairment of hearing, dizziness, headache and nausea. Gastro-intestinal disturbances are also observed at times and the ingestion of even small doses for a considerable period may be followed by gastric catarrh, and its sequelæ. The administration of larger doses has been followed by marked and at times persistent deafness and even blindness.

The habitual ingestion of coal-tar analgesics, which form para-aminophenol, is followed by a train of symptoms including destructive changes in the blood, the production of methæmoglobin, a degeneration of the heart muscle, cardiac failure, cyanosis, abnormally low temperature, and collapse.

The salicylates have many of the properties of coal-tar analgesics and are used quite extensively as sedatives for the relief of headache and neuralgic pains. They are known to have a deleterious influence on the digestive function and in larger doses or when long continued are frequently accompanied by symptoms of cinchonism similar to those produced by quinine. The salicylates may also have a depressing influence on the central nervous system accompanied by convulsions, slowing of respiration, and collapse from circulatory depression.

Pontius (*J. Am. M. Assoc.*, vol. 62, p. 797) reports seeing a nervous woman, age forty-five, who on the advice of a friend had for the past year taken five-grain tablets (one per dose) from three to ten times daily for neuralgic pains. Her mental condition when seen by the physician was similar to that of one addicted to the morphine habit.

The coal-tar hypnotics like sulphonal and trional may cause acute symptoms of poisoning accompanied by ataxia, nausea, gastric pain, irritation of the kidneys, albuminuria, and nephritis.

The mental state induced by the long-continued use of sulphonal and its congeners in full doses is said to be a badly disturbed one with derangement and even dementia.

The occurrence of acute intoxication in patients from the ingestion of various drugs is frequently ascribed to idiosyncrasy. As yet comparatively little is known regarding the principles underlying this

occasional manifestation of undue activity, but it is probable that idiosyncrasy, so called, is in reality due to the synergistic action of several compounds taken at the same time or to the combined action of products formed in the human body with a compound taken as medicine.

In connection with some drugs, the use of which is long continued, the body may develop a tolerance or diminished sensitiveness to their action. This appears to be particularly true of narcotics and of many of the cathartic drugs. These lead to the habitual consumption of drugs, and their use once commenced is fraught with many difficulties. That the use of the so-called laxative drugs is not an entirely negligible factor is well shown by the table presented above, which enumerates the quantities of a few of the drugs of this type that are consumed annually in this country.

The amount of money expended annually for drugs and medicines in this country is out of all proportion to the real need or requirements of the people, and to this extent at least the unnecessary use of medicines may be considered an economic waste.

Enough has been said to demonstrate that medicines if at all deserving of the name must of necessity be harmful when misapplied or when used for any considerable length of time without a due appreciation of their possible secondary influences and the chronic derangements that may follow in their wake.

The rapid increase in mortality from degenerative diseases and the fact that this increase is greatest in persons who should be in the prime of life would warrant making a careful study of the problems involved with the view of directing attention to the causative factors of the degenerative processes.

CURRENT LITERATURE.

The Druggist as Seen by the Governor of Minnesota.

In the address of Governor W. S. Hammond, of Minnesota, before the Thirty-first Annual Convention of the Minnesota State Pharmaceutical Association, February 9, in St. Paul, he said:

"The pharmacist is a great deal more than the apothecary of old or the druggist of even more recent days. There was a time when the apothecary shop, the drug store—either—was a sort of gather-as-you-please to gossip over the events of the day and incidentally and between times compound various medicinal preparations. The work of the apothecary was a particular and technical kind of work,

and there was so little of it that the compensation necessarily was quite large. But there has come a great change in more recent years. The pharmacist is the scientific man that the apothecary was of old. He is the technical compounder, the registered druggist, but he is more of a business man than his predecessors were, and because of that fact the people, those who trade with the pharmacist, have been the gainers. The whole calling itself seems to have taken on another form. I imagine there is not so much compounding to-day as there was a few years ago. Great establishments like Wyeth's and Parke, Davis & Co. do a great deal of the work that the old-time apothecary did. Now, under these changing conditions, it is very, very advisable, it seems to me, that there should be frequent meetings for communication of ideas and thoughts relating to the business among the pharmacists of the State. The pharmacist has become a business man; he has always been a business man, but I am inclined to think that to-day he is more of a business than professional man, while some time ago it seems to me he was more of the professional man than the business man. Now, is there any danger growing out of this? Is there anything that you ought to think about in connection with this change, if I am correctly advised and my conclusions are warranted by the facts? It would be unfortunate if this old-time honorable profession should become merely business. So much of the sentiment, so much of the romance would be taken away that we might feel somewhat sad at the change, but more than mere sentiment, more than mere romance, it would be another development of the dollar idea. I admire the successful business man. We cannot but be astonished at the great efforts of the captains of industry. We like the strong, pushing, virile business men who start with little or nothing, and build up gigantic enterprises, but they are business men. We would not want our lawyers, our doctors, out apothecaries, our clergymen to be distinguished principally as mere business men. We like to have them remain in the realm of professionalism, and be as great and as useful in professional work as others are in the business field. Now, I trust that with these great houses compounding so many of the things that the apothecaries themselves compounded not many years ago we will not have a change in this line of work, and that the apothecary may remain the professional instead of the business man, realizing, of course, the necessity of good judgment and of business skill in the conduct of any business enterprise, and yet there are very important matters connected with pharmacy that are wholly unrelated

to the mere question of bookkeeping and income and outgo. We are all interested, and you are particularly interested, in legislation tending to restrict the use of noxious drugs. Here is a line of endeavor that, of course, should be absolutely divorced from the business end of the work. Here is a question that appeals to you as professional men and as men who desire to adapt your profession to the best interest of your brothers and your sisters, and any attempt, I fear, to connect this kind of legislation with the business end of the pharmacist's occupation and profession would tend to detract from the high professional standard that the apothecary has always had, and that the modern pharmacist should endeavor to maintain. I am not a pharmacist, but a mere observer. I have spoken simply as a layman in a general way. My purpose in coming here was not to deliver a lecture. I could not hope to impart advice to men and women like yourselves who have studied the subject for years, but I may in a way represent the layman who looks upon the pharmacist as the majority of laymen do—who wishes him well and desires to see the time-honored and highly-respected profession maintain all that is good in it, and push on to higher and better results. I welcome this body here this morning. I repeat my greetings; I trust that you will accomplish much for yourselves and much for the benefit of your profession throughout the State and country."

New Beta-naphthol Reaction.

It has been observed that a fairly well-diluted solution of beta-naphthol in the presence of a relatively small quantity of nitrite gives a beautiful red-violet or red color. The reaction, which is stated to be useful for the detection of beta-naphthol in foodstuffs, is carried out as follows: A few drops of concentrated sulphuric acid are added to 1 c.c. of diluted beta-naphthol solution, and to this is added 0.05 c.c. of a 0.01 per cent. solution of sodium nitrite, when the above coloration is obtained. The reaction is sensitive in a solution containing 0.0002 per cent. of beta-naphthol. The coloration is supposedly due to a quinonoid derivative of beta-naphthol. —*The Chemist and Druggist,* Dec., 1914, p. 45.

Digestive Enzymes.

The *Journal of the A. M. A.* comments on a recent bulletin of the Bureau of Chemistry which speaks of the importance of determining exactly the activity of digestive enzymes and ferments. The

difficulty with such preparations is that they are most unstable; while active at first, they soon lose their digestive power. An examination of certain pharmaceutical preparations supposed to contain definite ferments showed that they contained little or none of these bodies. Where manufacturers had used proper amounts of the various enzymes, such as pepsin, pancreatin, diastase, and similar ferments, no attempt had been made to determine their activity. Manufacturers are warned by the Department of Agriculture, through the Bureau of Chemistry, that combinations claiming to contain digestive enzymes must be active when sold. Such preparations should be dated, and not sold after they become inactive. "The Council on Pharmacy and Chemistry nearly seven years ago called attention to the various digestive impossibilities on the market. Practically all of these are still sold. To sell a sick patient a mass of inert material which he believes to be active is not only perpetration of a fraud on the patient, but does gross injury to the physician who prescribes for him and endangers still further the patient's health. It is to be hoped that the government will adopt measures that will prevent the sale of such useless and scientifically absurd combinations."—*Jour. A. M. A.*, Dec., 19, 1914.

PHARMACEUTICAL MEETING.

At the Pharmaceutical Meeting held at the Philadelphia College of Pharmacy on Friday, January 15th, at 3 P.M., in the Chemical Lecture Room, Mr. Warren H. Poley presided and introduced Prof. Charles H. LaWall, who gave a talk upon the subject of Bermuda, which was occasioned by a recent visit to the island.

The talk was illustrated with lantern reproductions of nearly 100 photographs, which had been arranged in chronological order and which showed the principal features of interest, geographical, topographical, architectural, æsthetic, and scientific.

Views were shown of the growing plants which are of interest during the winter season, and specimens of some of the native fruits, including the pawpaw, were given especial attention. The lecture was remarkable in that no mention whatever was made of the three products for which Bermuda is particularly noted, viz., arrowroot, onions, and lilies. This omission was occasioned by the fact that arrowroot is no longer grown for the market, and the onion and lily crops are just being planted at this time of the year.